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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
JAISLE, CECILIA M

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,165	COLLINS ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2-26-2004, 5-28-2004 & 1-12-2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-20-2004 & 1-12-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The reference listings in the specification (pages 1-3, 12, 14, 16, 17, 25, 32, *inter alia*) are not a proper information disclosure statement, despite the paragraph bridging pages 32-33. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Many of these references appear to provide prior information regarding the claimed compounds and methods of treating CXCR3-mediated conditions. Applicants are required to provide a proper Information Disclosure Statement citing these references, as well as copies thereof for consideration in the examination of this application. 37 CFR 1.56. These references have not been considered on this record.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific compounds 103, 105, 107, 109 and 111 for treating multiple sclerosis, does not provide reasonable enablement for the

breadth of the claimed Formula (I) compounds for prevention and treatment of the various disorders recited in the claims, including those yet to be identified, as due to abnormal CXCR3 activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Balashov, et al. (CCR5+ and CXCR3+ T cells are increased in multiple sclerosis and their ligands MIP-1α and IP-10 are expressed in demyelinating brain lesions, Proc. Natl. Acad. Sci., Vol. 96, pp. 6873-6878, June 1999) report data that "provide a rationale for the use of agents that block CCR5 and/or CXCR3 as a therapeutic approach in the treatment of MS." The following reasons apply otherwise to this enablement rejection.

Claims 10-22 recite a method of treating a CXCR3-mediated condition, and claims 23-24 recite a method of treating or preventing a condition selected from neurodegenerative diseases, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, atherosclerosis, encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, psoriasis, eczema, uticaria, type I diabetes, asthma, conjunctivitis, otitis, allergic rhinitis, chronic obstructive pulmonary disease, sinusitis, dermatitis, inflammatory bowel disease, Behcet's syndrome, gout, cancer, viral infections, bacterial infections, organ transplant conditions and skin transplant conditions. The claimed scope includes the recited disorders as well as undiscovered disorders/conditions associated with abnormal CXCR3 activity for which there is no enabling disclosure. Also, the claimed scope includes prevention and treatment of various disorders/diseases, which are not adequately enabled based on modulation of abnormal

CXCR3 activity. The claimed compounds are disclosed to modulate abnormal CXCR3 activity and the specification recites that the claimed compounds are therefore useful to prevent and treat diseases caused or exacerbated by abnormal CXCR3 activity, such as all diseases recited for claims 10-24, for which Applicants provide no competent evidence. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests (pages 19-32, *inter alia*) are highly predictive for all uses disclosed and embraced by the claim language for the intended host. The disclosure in paragraph 00114 is prophetic only.

Many if not most diseases said to be prevented or controlled by the claimed compounds, for example, systemic lupus erythematosus, multiple sclerosis, cancer, etc., are known as difficult to treat. At present no known drug successfully prevents or reverses the course of many of these diseases, despite the fact that many drugs are said to modulate abnormal CXCR3 activity. Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* The disclosure in this application is not sufficient to enable the instantly claimed methods based solely on mediation of abnormal CXCR3 activity. The state of the art

indicates the requirement for undue experimentation. In regard to neurodegenerative diseases, such as Alzheimer's disease, Xia, et al. (Expression of the chemokine receptor CXCR3 on neurons and the elevated expression of its ligand IP-10 in reactive astrocytes: in vitro ERK1/2 activation and role in Alzheimer's disease, J. of Neuroimmunology, 108, 2000, 227-235) demonstrated "for the first time the constitutive presence of the chemokine reception, CXCR3, in neurons, and the expression of its ligand, IP-10, in a subpopulation of astrocytes," suggesting that "chemokines may also play a role in normal brain functions and in diseases of the CNS." In regard to systemic lupus erythematosus, Shiozawa, et al. (Enhanced expression of interferon-inducible protein 10 associated with Th1 profiles of chemokine receptor in autoimmune pulmonary inflammation of MRL/*lpr* mice, Arthritis Research & Therapy, Vol. 6, No. 1, 2003, R78-R86) suggested that "IP-10 expression in the lung is involved through CXCR3, in the pathogenesis of pulmonary inflammation associated with migration of Th1 cells," and concluded that they "did not provide a direct demonstration of the role of the IP-10/CXCR3 pathway in the pathogenesis of pulmonary infiltration in MRL/*lpr* mice, and at present it is difficult to answer how the *lpr* gene abnormality is associated with preferential activation of Th1 responses." Regarding encephalitis, Trebst, et al. (Chemokine receptors on infiltrating leucocytes in inflammatory pathologies of the central nervous system, Neuropathology & Applied Neurobiology, 2003, 29, 584-595) observed, "CXCR3 was highly, but not invariably, associated with CD3 immunoreactive cells..." Regarding atherosclerosis, Veillard, et al. (Differential Influence of Chemokine Receptors in CCR2 and CXCR3 in Development of Atherosclerosis In Vivo, J. of the

Am. Heart Assn., 2006, 112, 870-878) demonstrated that "the chemokine receptor CXCR3 is of minor importance for the development of advanced complicated atherosclerotic lesions." Thus, the ability of an agent that mediates abnormal CXCR3 production to prevent or ameliorate all of the diseases/conditions recited by the present claims remains open to further study and proof.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. Breadth of the claims: The claims embrace all conditions, including ones yet to be determined, related to mediating abnormal CXCR3 activity.
2. Nature of the invention: Therapeutic use of the claimed compounds in preventing and treating diseases/conditions related to abnormal CXCR3 activity.

3. State of the prior art: See the discussion *supra* of Xia, Shiozawa, Trebst, and Veillard, as contrasted with Balashov.

4. Level of predictability in the art: Applicants do not provide highly predictive competent evidence or recognized tests to prevent and treat all conditions recited for the claimed compounds. Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

> "The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (Fed.Cir. 2003).

5. Amount of direction provided; and (6) presence of working examples: The working examples of the specification do not show prevention and treatment of all recited conditions/diseases. The state of the art (e.g., Xia, Shiozawa, Trebst, and Veillard, as contrasted with Balashov) supports that successful prevention and treatment of conditions caused or exacerbated by abnormal CXCR3 activity is a subject for further investigation.

7. Quantity of experimentation needed to make or use the invention, based on the content of the disclosure, would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.

The consideration of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the breath of the claims, the pharmaceutical nature of the invention, the unpredictability of the relationship between CXCR3 activity and specific diseases/conditions, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims. Note also paragraph 00114 specifically inviting further experimentation.

The Supreme Court has recognized that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 148 USPQ 689, 696 (U.S. 1966). See also *In re Genentech, Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (Fed.Cir. 1997)("patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.")

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration clearly justifies that conclusion here and undue experimentation would be required to practice Applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7, 12-22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 5 and 6 recite the limitations "R is a saccharide or a saccharide derivative" and "R is glucoronide". There is insufficient antecedent basis for these limitations in claim 1. In regard to claim 5, the term "saccharide derivative" is open ended, because it is not understood what is intended by the term "derivative." The specification does not define what is covered by this term.

Regarding claim 7, claim 1 does not provide antecedent basis for the third and fourth compounds. Claim 12 is broader than claim 1. Claims 12-22 recite "a method of treating ... comprising administering ... a ... compound according to formula (II)," while claim 1 excludes the formula (II) compound. Claim 24 has the same discrepancy.

Rejections Under 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of the

obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Medina, et al., WO 02/083143, published Oct. 24, 2002 and entitled (under 35 U.S.C. 102(b)) to the effective date of Dec. 11, 2001 (hereinafter, Medina I), taken alone and further in view of Bridger, et al., US Pat. Appl. Pub. 2003/0028023, published February 6, 2003 (hereinafter, Bridger). Medina I describes pyrido-pyrimidones (col. 14, line 43 – col. 16, line 63, *inter alia*) that encompass the compounds of the present claims. See also the Medina I compounds 3.16a, 3.16b, 3.17, 3.20, 3.50, 3.62, 3.70 and 3.74. Medina I shows that the R-substituent of the presently claimed compounds of Formula (I), may be (C1-C8) alkoxy (col. 15, lines 51-55). Compounds of the present claims wherein R is hydrogen or alkoxy of more than 8 carbon atoms would be obvious over the specific compounds of Medina I as alkyl homologs thereof. Likewise, compounds of the present claims that are position isomers of the specific compounds of Medina I

would be obvious thereover. In regard to the N-oxide forms of the presently claimed compounds, Bridger teaches (paragraph 0081, *inter alia*) that, in structurally similar compounds that modulate α-chemokines, CXCR, nitrogen-containing heteroaromatic rings in the active compounds may equivalently be in the N-oxide form.

It would have been obvious to one of ordinary skill in the art at the time the present invention was made to modify the Medina I compounds to prepare the alkyl homologs and position isomers. It would also have been obvious to one of ordinary skill in the art at the time of the present invention to modify the Medina I compounds to prepare the N-oxides, as suggested by Bridger. One of ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous and isomeric compounds are expected to possess similar properties. One of ordinary skill in the art would have been motivated to prepare the instantly claimed N-oxide compounds because Bridger indicates that such derivatives retain the expected pharmaceutical function. It has been held that compounds that are structurally homologous and isomeric to prior art compounds are *prima facie* obvious, absent a showing of unexpected results.

> An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.

In re Payne, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 16 USPQ2d 1897 (Fed.Cir. 1991) (discussed in MPEP § 2144) for an extensive case law review of obviousness based on close structural

chemical compound similarity. See MPEP § 2144.08, ¶ II.A.4(c). Compounds which are homologs (compounds differing regularly by the successive addition or subtraction of the same chemical group, e.g., by -CH3 or lower alkyl groups), as here, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 195 USPQ 426 (CCPA 1977).

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-24 are rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over each of Medina, claims 1-40, US Pat. No. 6,794,379, issued Sept. 21, 2004 (hereinafter, Medina II), Huang, et al., claims 1-28, US Pat. 6,964,967, issued Nov. 15, 2005 (hereinafter, Huang), and Medina, claims 1-20, US

Pat. 7,067,662, issued June 27, 2006 (hereinafter, Medina III), each taken separately and further in view of Bridger. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are directed to compounds and methods of using those compounds, wherein the compounds are homologs and/or position isomers of compounds of the Medina disclosures and the Huang disclosure. The Medina and Huang disclosures are the all same but the claims are different, therefore the discussion *supra* of Medina I applies, *mutatis mutandi*, to Huang and each of the other Medina disclosures. The Bridger disclosure has been discussed *supra* and that discussion is repeated here as equally pertinent. The discussion of methyl and alkyl homologs and position isomers set forth above is repeated here as equally pertinent.

Claims 1-24 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Medina, et al., Serial No. 11/332,054, claims 1, 66, 91, 134 and 135 (hereinafter Medina IV), and Medina, et al., Serial No. 11/385,046, claims 1-21, 44, 45, 51, 52, 55-80, 83-111 and 114-135, hereinafter, Medina V), each taken separately and further in view of Bridger. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are directed to compounds and methods of using those compounds, wherein the compounds are homologs and/or position isomers of compounds of the Medina disclosures and the Huang disclosure. The Medina and Huang disclosures are the all same but the claims are different, therefore the discussion

supra of Medina I applies, *mutatis mutandi*, to Huang and each of the other Medina disclosures. The Bridger disclosure has been discussed *supra* and that discussion is repeated here as equally pertinent. The discussion of methyl and alkyl homologs and position isomers set forth above is repeated here as equally pertinent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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